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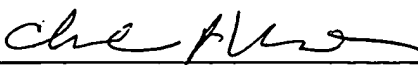
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application, to remove multiple dependency from the claims and to conform the claims to the American practice.

Respectfully submitted,  
BIERMAN, MUSERLIAN AND LUCAS

  
Charles A. Muserlian, #19,683  
Attorney for Applicant(s)  
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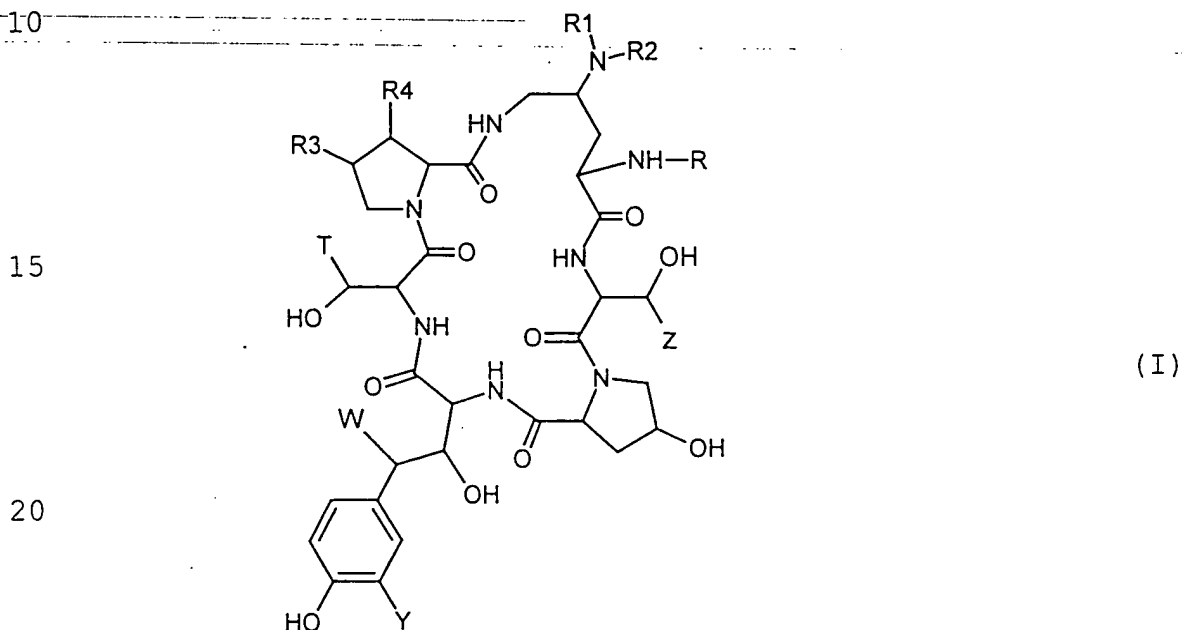
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New derivatives of echinocandine, their preparation process  
and their use as antifungals.

---This application is a 371 of PCT/FR00/01569 filed June 8, 2000.---

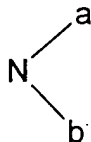
The present invention relates to new derivatives of  
5 echinocandine, their preparation process and their use as  
antifungals.

A subject of the invention is in all the possible isomer  
forms as well as their mixtures, the compounds of formula  
(I):



25 in which

either  $R_1$  and  $R_2$  identical to or different from one another,  
represent a hydrogen atom, a hydroxyl radical, a linear,  
branched or cyclic alkyl radical containing up to 8 carbon  
atoms optionally interrupted by an oxygen atom optionally  
30 substituted by a halogen atom, an OH radical, an



35 radical, a and b identical to or different from one another,  
representing a hydrogen atom or an alkyl radical containing  
up to 8 carbon atoms, a and b can optionally form with the  
nitrogen atom a heterocycle optionally containing one or more

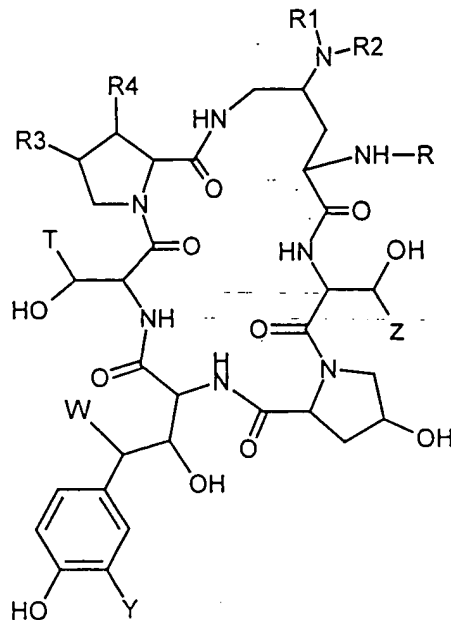
*As group selected from the group consisting of*

1) ~~in~~ all possible isomeric forms ~~as well as~~ <sup>and</sup> their mixtures ~~of~~ the compounds ~~of~~ <sup>the</sup> formula (I).

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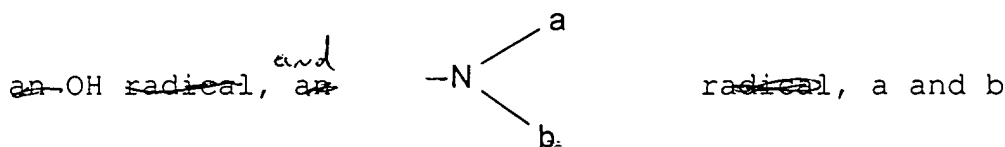
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(I)

20 ~~wherein~~ <sup>are individually selected from the group consisting of</sup>  
~~in which~~ either R<sub>1</sub> and R<sub>2</sub> ~~identical to or different from one another,~~  
~~represent a hydrogen atom, a hydroxyl radical, a linear,~~ <sup>alkyl and</sup>  
~~branched or cyclic alkyl radical containing up to 8 carbon~~  
~~atoms optionally interrupted by an oxygen atom optionally~~  
~~substituted by a halogen atom,~~ <sup>and</sup>  
 25 ~~substituted by a halogen atom,~~ <sup>a member selected from the group consisting of</sup>



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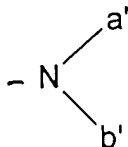
~~are individually~~ <sup>of 1</sup>  
~~identical to or different from one another,~~  
~~representing a hydrogen atom or an alkyl radical containing~~  
~~up to 8 carbon atoms,~~ <sup>or</sup> a and b can optionally form with the  
~~nitrogen atom a heterocycle optionally containing one or more~~ <sup>at least</sup>  
 35 ~~additional heteroatoms,~~  
 or R<sub>1</sub> forms with the endocyclic carbon atom

carrying ~~the~~  $\begin{array}{c} \text{R1} \\ | \\ -\text{N} \\ | \\ \text{R2} \end{array}$  ~~radical~~ a double bond and ~~or~~ R2

5

<sup>is selected from the group consisting of</sup>  
~~represents an-XRa radical, X representing an oxygen, atom or~~  
~~an-NH- or-N-alkyl radical containing up to 8 carbon atoms and~~  
~~Ra represents a hydrogen atom, a linear, branched or cyclic~~  
~~alkyl radical containing up to 8 carbon atoms optionally~~

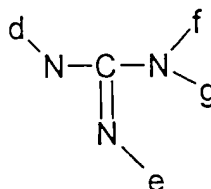
10 substituted by <sup>at least one member of the group consisting of</sup> ~~one or more halogen atoms, by one or more-OH,~~  
~~-CO<sub>2</sub>H, -CO<sub>2</sub>alk, radicals, by an~~



15

~~radical, a' and b' representing a hydrogen atom, or an alkyl~~  
~~radical containing up to 8 carbon atoms, a' and b' can form a~~  
~~heterocycle optionally containing one or more additional~~  
~~heteroatoms and/or by a heterocycle containing one or more~~

20 heteroatoms or R<sub>2</sub> <sup>is</sup> ~~represents a~~

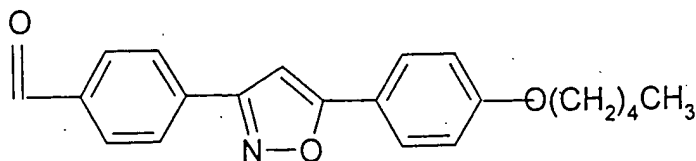


25 ~~radical in which d, e, f and g represent a hydrogen atom or~~  
~~an alkyl radical containing up to 8 carbon atoms, f and g can~~  
~~moreover represent an acyl radical containing up to 8 carbon~~  
~~atoms, e and f can also form a ring optionally containing one~~  
~~or more heteroatoms,~~

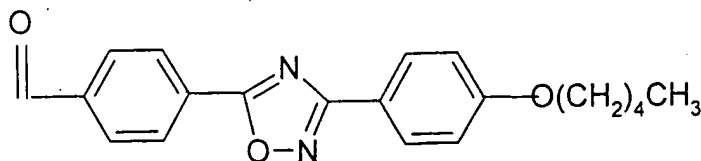
30 ~~R<sub>3</sub> represents a hydrogen atom, a methyl or hydroxyl radical~~

~~R<sub>4</sub> represents a hydrogen atom or a hydroxyl radical~~

~~R represents a radical chosen from the following radicals:~~

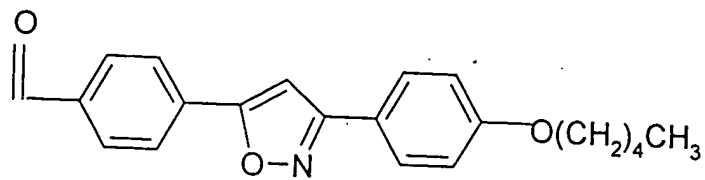


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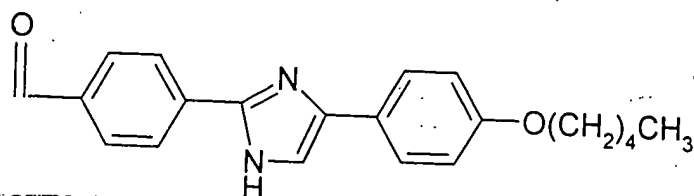


*is selected from the group consisting of*

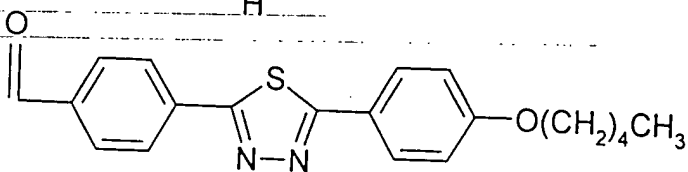
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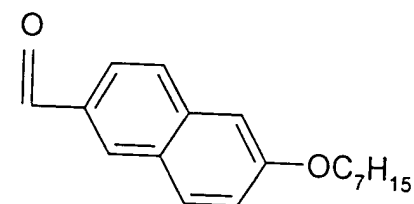
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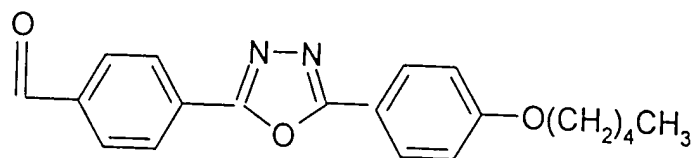
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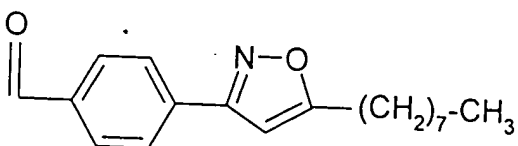
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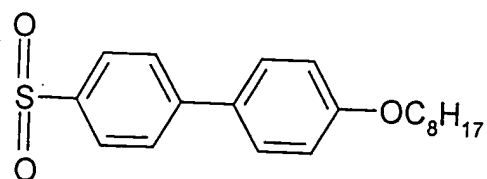
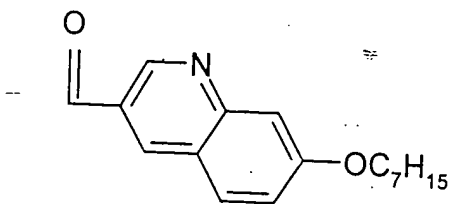
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and

*is selected from the group consisting of*

T represents a hydrogen atom, a methyl radical, a  $-\text{CH}_2\text{CONH}_2$ ,  $-\text{CH}_2\text{CN}$  radical, a  $-(\text{CH}_2)_2\text{NH}_2$  or  $-(\text{CH}_2)_2\text{Nalk}^+\text{X}^-$  radical, X being a halogen atom and alk an alkyl radical containing up to 8 carbon atoms,

5 Y represents a hydrogen atom, a hydroxyl radical or a halogen atom <sup>and</sup> an  $\text{OSO}_3\text{H}$  radical <sup>and</sup> one of the salts <sup>means</sup> of this radical, W represents a hydrogen atom or an  $-\text{OH}$  radical,

Z represents a hydrogen atom or a methyl radical <sup>and a non-toxic, pharmaceutically acceptable acid</sup> as well as the addition salts <sup>means</sup> with acids of the products of

10 formula (I).

2) ~~The~~ compounds of formula (I) defined in claim 1 in which T represents a hydrogen atom.

3) ~~The~~ compounds of formula (I) defined in claim 1 or 2 in which W represents a hydrogen atom.

15 4) ~~The~~ compounds of formula (I) defined in any one of claims 1 to 3, in which Z represents a methyl radical.

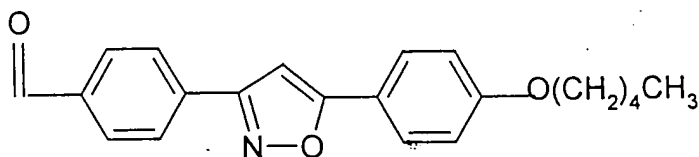
5) ~~The~~ compounds of formula (I) defined in any one of claims 1 to 4 in which Y represents a hydrogen atom.

6) ~~The~~ compounds of formula (I) defined in any one of claims 1 to 5 in which  $\text{R}_3$  represents a methyl radical.

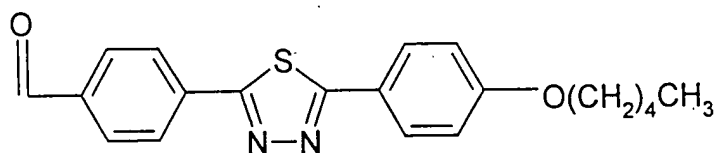
20 7) ~~The~~ compounds of formula defined in <sup>claim 1</sup> any one of claims 1 to 6, in which  $\text{R}_4$  represents a hydroxyl radical.

8) ~~The~~ compounds of formula (I) defined in any one of claims 1 to 7 in which R represents a <sup>is selected from the group consisting of</sup>

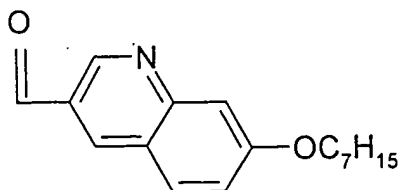
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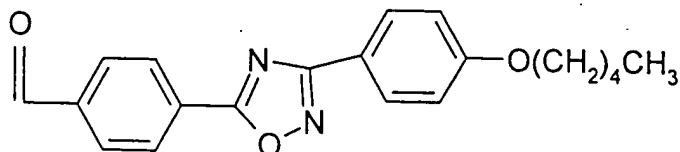
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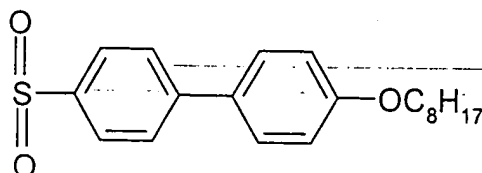
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~~radical~~  
~~or a~~

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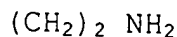
and

15 ~~radical.~~

9) The compounds of formula I defined in any one of claims 1 to 8 in which  $R_1$  represents a hydrogen radical.

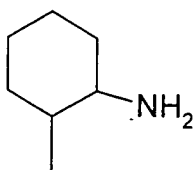
10) The compounds of formula defined in any one of claims 1 to 9 in which  $R_2$  represents a

20

~~radical.~~

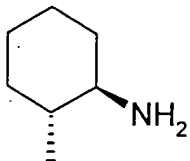
11) The compounds of formula I defined in any one of claims 1 to 9 in which  $R_2$  represents a

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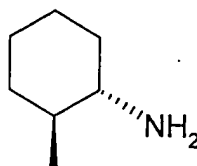
~~radical and in particular the~~

20. A compound of claim 11 wherein  $R_2$  is

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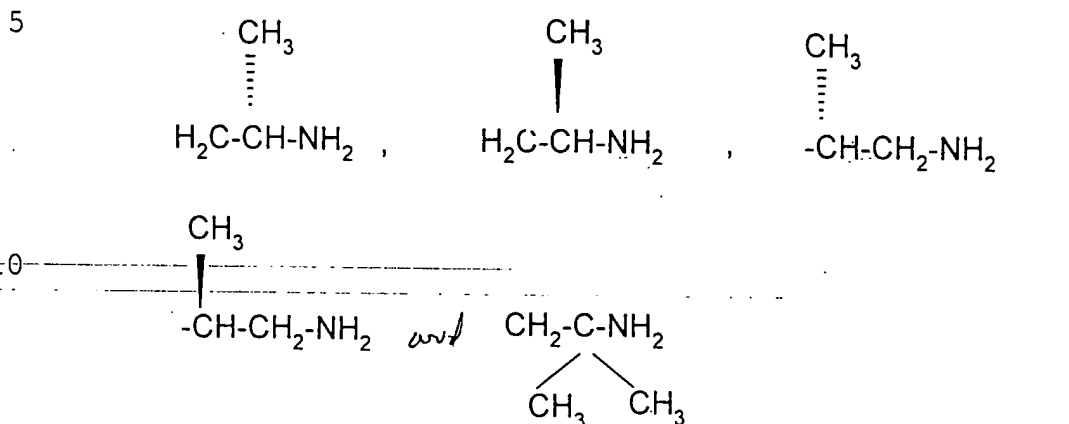
or





~~radicals.~~

- 12 ~~12) The compounds of formula I defined in any one of claims 1 to 9 in which R<sub>2</sub> represents a group consisting of~~ <sup>is selected from</sup>



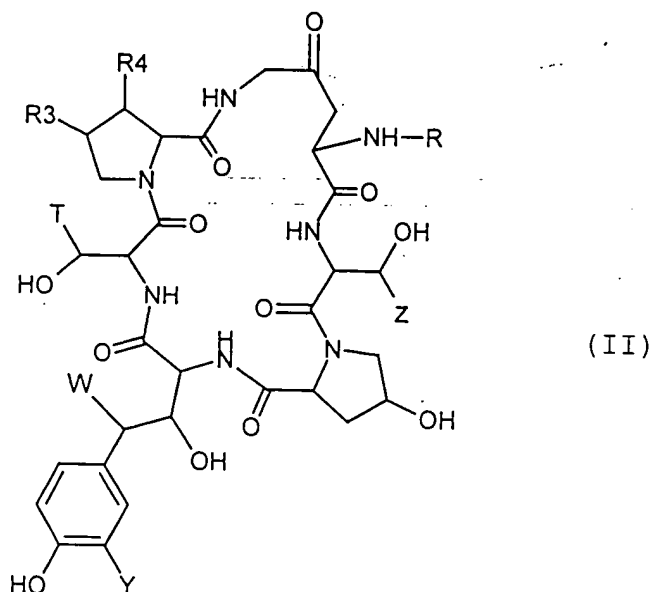
15 ~~radical.~~

- 13 ~~13) The compounds of formula I defined in claim 1 the names of which follow:~~ <sup>selected from</sup>

- 1-[4-[(2-aminoethyl)-amino]-N2-[[4-[5-[4-(pentyloxy)-phenyl]-3-isoxazolyl]-phenyl]-carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandine B trifluoroacetate,
- trans-1-[4-[(2-aminocyclohexyl)-amino]-N2-[[4-[5-[4-(pentyloxy)-phenyl]-3-isoxazolyl]-phenyl]-carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandine B trifluoroacetate,
- 1-[4-[(2(S)-aminopropyl)-amino]-N2-[[4-[5-[4-(pentyloxy)-phenyl]-3-isoxazolyl]-phenyl]-carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandine B trifluoroacetate,
- 1-[4-[(2-aminoethyl) amino]-N2-[[4-[5-[4-(pentyloxy)-phenyl]-1,3,4-thiadiazol-2-yl]-phenyl]-carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandine B trifluoroacetate,
- trans 1-[4-[(2-aminocyclohexyl)-amino]-N2-[[4-[5-[4-(pentyloxy)-phenyl]-1,3,4-thiadiazol-2-yl]-phenyl]-carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandine B trifluoroacetate and
- trans 1-[4-[(2-aminocyclohexyl)-amino]-N2-[[4-[3-[4-

(pentyloxy enyl]-1,2,4-oxadiazol-5-yl]-phenyl]-carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandine B trifluoroacetate.

14 ~~1A) A process for the preparation of the compounds of formula~~  
 5 ~~(I) defined in any one of claims 1 to 13, characterized in~~  
~~that a compound of, formula (II)~~



in which R, R<sub>3</sub>, R<sub>4</sub>, T, Y, W and Z ~~are defined as in claim 1~~ <sup>are defined as in claim 1</sup> retain their previous meaning, ~~is subjected to the action of~~ <sup>with</sup> an amine or of an amine derivative capable of introducing

the  $\begin{array}{c} \text{R}_1 \\ \diagup \\ \text{N} \\ \diagdown \\ \text{R}_2 \end{array}$  radical in which R<sub>1</sub> and R<sub>2</sub> ~~are defined as in claim 1~~ <sup>are defined as in claim 1</sup>

30 ~~retain their previous meaning and if desired to the action of~~ <sup>optionally then with</sup>  
 a reducing agent,  
 and/or ~~of~~ a functionalization agent of the amine,  
 and/or ~~of~~ an acid ~~in order to form the salt of the product~~  
~~obtained,~~  
 35 and/or ~~of~~ a separation agent of the different isomers  
 obtained.  
 and in this way the compound of formula (I) as defined in  
 claim 1 is obtained.

15 ~~As chemical products, the compounds of formula (II)~~ <sup>the</sup> ~~wherein R, R<sub>3</sub>, R<sub>4</sub>, T, Y, W and Z are defined as in claim 14.~~ <sup>(insert)</sup>

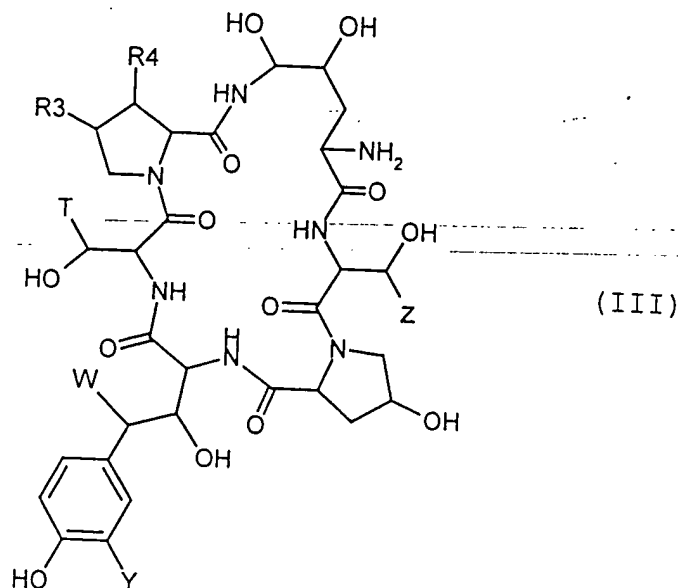
16) A process according to claim 14 <sup>wherein</sup> characterized in that a compound, formula (III)

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of the

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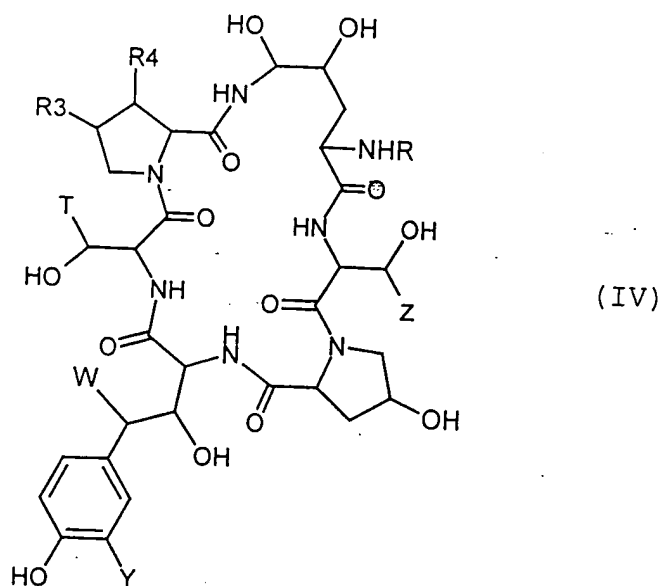


20 ~~R<sub>3</sub>, R<sub>4</sub>, T, W, Y and Z are defined as in claim 14~~  
~~in which the different substituents retain their previous~~  
~~meaning is subjected to the action of an agent capable of~~  
~~replacing -NH<sub>2</sub> by -NHR, R retaining its previous meaning in~~  
~~order to obtain the compound of formula (IV)~~

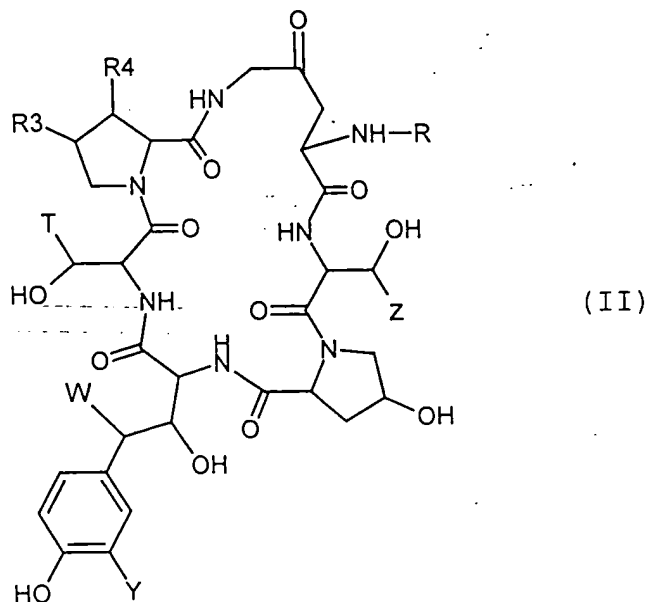
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*Reacting said compound with*  
 which is subjected to the action of trimethylsilyl iodide in  
 order to obtain the corresponding compound of formula ~~(II)~~



17) As new chemical products the compounds of formula III and IV defined in claim 16.

20 18) As antifungal compounds, the compounds of formula (I) defined in any one of claims 1 to 13, as well as their addition salts with acids.

19) The pharmaceutical compositions containing at least one compound of formula (I) defined in any one of claims 1 to 13 as a medicament, as well as their addition salts with pharmaceutically acceptable acids.